Supporting Information
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Supporting information for

The first example of azole-fused cyclic anhydride reacting in the Castagnoli-Cushman way

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General information

NMR spectroscopic data were recorded with Bruker Avance 400 spectrometer (400.13 MHz for $^1$H and 100.61 MHz for $^{13}$C) in DMSO-$d_6$ and in CDCl$_3$ and were referenced to residual solvent proton signals ($\delta_H = 7.26$ and 2.50 ppm, respectively) and solvent carbon signals ($\delta_C = 77.0$ and 39.5 ppm, respectively). Melting points were determined with a Stuart SMP50 instrument in open capillary tubes. Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Chlorobenzene was distilled from P$_2$O$_5$ and stored over molecular sieves 4Å.

Imines were prepared from corresponding aldehydes and amines by stirring with anhydrous MgSO$_4$ at room temperature in DCM for 24-48 h and subsequent concentration in vacuo. All imines were stored at 5 °C in darkness.

Preparation of pyrazoles 9a-e

**General procedure.** To a stirred solution of appropriate methyl ketone (0.1 mol) in dry toluene (200 mL) was added a suspension of NaH in mineral oil (60%; 0.2 mol) in portions and the mixture was warmed to 50 °C. At this temperature a solution of diethyl oxalate (0.15 mol) in dry toluene (60 mL) was added dropwise under stirring. The reaction mixture was refluxed for 1.5 h. Upon cooling to room temperature acetic acid (0.25 mol) was added dropwise. The reaction mixture was washed with water (200 mL), organic phase was dried over MgSO$_4$ and evaporated to dryness. The obtained crude diketone was dissolved in ethanol (250 mL), hydrazine dihydrochloride (0.11 mol) was added and the mixture was refluxed for 3 h. After evaporation of solvent the residue was treated with water (200 mL) and kept under ice-cooling for 1 h. Crystals were filtered off and dried in air to afford the corresponding pyrazole. In some cases thus obtained substance was purified by recrystallization from aqueous ethanol.

**Ethyl 3-(p-tolyl)-1H-pyrazole-5-carboxylate (9a).**

Yield 19.6 g (85%), colorless crystals. $^1$H NMR (400 MHz, CDCl$_3$+DMSO-$d_6$ (5:1)) $\delta$ 7.59 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 6.93 (s, 1H), 5.93 (br.s, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.30 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H).

**Ethyl 3-(4-fluorophenyl)-1H-pyrazole-5-carboxylate (9b).**

Yield 16.8 g (72%). $^1$H NMR (400 MHz, CDCl$_3$+DMSO-$d_6$ (5:1)) $\delta$ 8.90 (br.s, 1H), 7.69 (dd, $J = 8.8$, 5.3 Hz, 2H), 7.02 (t, $J = 8.7$ Hz, 2H), 6.94 (s, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H).

**Ethyl 3-(3,4-dimethoxyphenyl)-1H-pyrazole-5-carboxylate (9c).**

Yield 12.7 g (46%) after recrystallization. $^1$H NMR (400 MHz, CDCl$_3$+DMSO-$d_6$ (5:1)) $\delta$ 7.84 (br.s, 1H), 7.32 (d, $J = 2.0$ Hz, 1H), 7.25 (dd, $J = 8.3$, 2.0 Hz, 1H), 6.92 (s, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H).
Ethyl 3-(thiophen-2-yl)-1H-pyrazole-5-carboxylate (9d).\(^4\) Yield 8.9 g (40%) after recrystallization. \(^1\)H NMR (400 MHz, CDCl\(_3\)+DMSO-d\(_6\) (5:1)) \(\delta\) 7.33 (dd, \(J = 3.6, 1.0\) Hz, 1H), 7.21 (dd, \(J = 5.1, 1.0\) Hz, 1H), 6.99 (dd, \(J = 5.1, 3.6\) Hz, 1H), 6.85 (s, 1H), 5.90 (br.s, 1H), 4.30 (q, \(J = 7.1\) Hz, 2H), 1.33 (t, \(J = 7.1\) Hz, 3H).

Ethyl 3-(tert-butyl)-1H-pyrazole-5-carboxylate (9e).\(^4\) Yield 11.0 g (59%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.67 (s, 1H), 6.28 (br.s, 1H), 4.40 (q, \(J = 7.1\) Hz, 2H), 1.41 (t, \(J = 7.1\) Hz, 3H), 1.37 (s, 9H).

Preparation of diesters 10 a-e and diacids 11a-e

**General procedure.** A mixture of corresponding pyrazole 9 (0.04 mol), ethyl chloroacetate (0.06 mol) and K\(_2\)CO\(_3\) (0.08 mol) in dry acetonitrile (100 mL) was stirred at 85 °C for 15–20 h (controlled by TLC). The solvent was evaporated and the mixture was treated with water (150 mL) and extracted with EtOAc (2×100 mL). Organic phase was dried over Na\(_2\)SO\(_4\) and evaporated to give crude mixture of regioisomers which was subjected to column chromatography on silica gel.

The obtained diester 10 (0.01 mol) was dissolved in THF (10 mL per 1.0 g), aqueous NaOH (0.03 mol in 50 mL of water) was added and the mixture was stirred at room temperature for 16 h. The resulting solution was extracted with ether (100 mL), organic layer was separated and discarded. The aqueous phase was cooled in ice, acidified with 6N HCl to pH 4 and stirred at 5 °C for 30 min. The crystalline precipitate was filtered, washed with water (30 mL) and dried in air. In case of oily precipitate it was extracted with EtOAc (2×75 mL), dried over MgSO\(_4\), evaporated and triturated with n-hexane. Crystals formed were filtered and dried in air to give pure diacid 11.

Ethyl 1-(2-ethoxy-2-oxoethyl)-3-(p-tolyl)-1H-pyrazole-5-carboxylate (10a). Eluent for chromatography n-hexane/EtOAc/DCM (5:1:1); yield 4.04 g (32%); colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.72 (d, \(J = 8.2\) Hz, 2H), 7.24 (d, \(J = 7.9\) Hz, 2H), 7.19 (s, 1H), 5.36 (s, 2H), 4.37 (q, \(J = 7.1\) Hz, 2H), 4.26 (q, \(J = 7.1\) Hz, 2H), 2.40 (s, 3H), 1.41 (t, \(J = 7.1\) Hz, 3H), 1.30 (t, \(J = 7.1\) Hz, 3H).\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\)
167.9, 159.8, 150.8, 138.0, 134.1, 129.5, 129.4, 125.6, 108.2, 61.7, 61.2, 53.6, 21.3, 14.2, 14.1. HRMS m/z [M+H]+ calcd for C_{17}H_{21}N_{2}O_{4} 317.1496, found 317.1488.

![Diagram](image)

1-(Carboxymethyl)-3-(p-tolyl)-1H-pyrazole-5-carboxylic acid (11a). Prepared from 0.015 mol of diester 10a; yield 3.55 g (91%); colorless solid. {^1}H NMR (400 MHz, DMSO-\textsubscript{d6}) δ 13.43 (br.s, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.10 (s, 1H), 5.12 (s, 2H), 2.33 (s, 3H). \textsuperscript{13}C NMR (101 MHz, DMSO-\textsubscript{d6}) δ 170.0, 161.9, 149.1, 138.8, 137.5, 130.3, 129.7, 125.5, 107.1, 54.6, 21.3. HRMS m/z [M+Na]+ calcd for C_{13}H_{12}N_{2}NaO_{4} 283.0689, found 283.0677.

![Diagram](image)

Ethyl 1-(2-ethoxy-2-oxoethyl)-3-(4-fluorophenyl)-1H-pyrazole-5-carboxylate (10b). Eluent for chromatography n-hexane/EtOAc/DCM (5:1:1); yield 4.6 g (36%); colorless solid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.80 (dd, J = 8.9, 5.4 Hz, 2H), 7.16 (s, 1H), 7.11 (t, J = 8.8 Hz, 2H), 5.36 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 167.8, 162.8 (d, J = 247.2 Hz), 159.6, 149.8, 134.3, 128.5 (d, J = 3.2 Hz), 127.4 (d, J = 8.2 Hz), 115.6 (d, J = 21.7 Hz), 108.2, 61.7, 61.3, 53.6, 14.2, 14.1. HRMS m/z [M+Na]+ calcd for C_{16}H_{17}FN_{2}NaO_{4} 343.1065, found 343.1050.

![Diagram](image)

1-(Carboxymethyl)-3-(4-fluorophenyl)-1H-pyrazole-5-carboxylic acid (11b). Prepared from 0.01 mol of diester 10b; yield 2.16 g (82%); colorless solid. \textsuperscript{1}H NMR (400 MHz, DMSO-\textsubscript{d6}) δ 13.21 (br.s, 2H), 7.90 (dd, J = 8.9, 5.5 Hz, 2H), 7.36 (s, 1H), 7.26 (t, J = 8.9 Hz, 2H), 5.26 (s, 2H). \textsuperscript{13}C NMR (101 MHz, DMSO-\textsubscript{d6}) δ 169.7, 162.5 (d, J = 244.7 Hz), 161.0, 148.7, 135.6, 129.2 (d, J = 3.0 Hz), 127.7 (d, J = 8.2 Hz), 116.1 (d, J = 21.6 Hz), 108.4, 53.8. HRMS m/z [M+Na]+ calcd for C_{12}H_{9}FN_{2}NaO_{4} 287.0439, found 287.0439.

![Diagram](image)

Ethyl 3-(3,4-dimethoxyphenyl)-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-5-carboxylate (10c). Prepared from 0.03 mol of pyrazole 9e; eluent for chromatography n-hexane/EtOAc/DCM (5:1:1, 3:1:1, 2:1:1); yield 5.65 g (52%); colorless solid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.40 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 8.3, 2.0 Hz, 1H), 7.14 (s, 1H), 6.91 (d, J = 8.3 Hz, 1H), 5.34 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 167.9, 159.7, 150.6, 149.24, 149.18, 134.1, 125.4, 118.4, 111.2, 108.8, 108.0, 61.7, 61.2, 55.94, 55.93, 53.5, 14.2, 14.1. HRMS m/z [M+H]+ calcd for C_{18}H_{23}N_{2}O_{6} 363.1551, found 363.1561.
1-(Carboxymethyl)-3-(3,4-dimethoxyphenyl)-1H-pyrazole-5-carboxylic acid (11c). Prepared from 0.01 mol of diester 10c; yield 2.97 g (97%); colorless solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.10 (br.s, 2H), 7.41 – 7.31 (m, 2H), 7.31 (s, 1H), 6.99 (d, J = 8.1 Hz, 1H), 5.24 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H). ¹³C NMR (101 MHz, DMSO-d₆) δ 169.8, 149.4, 149.3, 135.6, 125.5, 118.2, 112.4, 109.2, 108.1, 55.99, 55.98, 53.8. HRMS m/z [M+Na]⁺ calcd for C₁₄H₁₄N₂NaO₆ 329.0744, found 329.0753.

Ethyl 1-(2-ethoxy-2-oxoethyl)-3-(thiophen-2-yl)-1H-pyrazole-5-carboxylate (10d). Prepared from 0.03 mol of pyrazole 9d; eluent for chromatography n-hexane/EtOAc/DCM (5:1:1, 3:1:1, 2:1:1); yield 3.8 g (41%); yellowish viscous oil. ¹H NMR (400 MHz, CDCl₃) δ 7.37 (dd, J = 3.6, 1.1 Hz, 1H), 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.10 (s, 1H), 7.08 (dd, J = 5.1, 3.6 Hz, 1H), 5.33 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.7, 159.5, 146.1, 135.3, 134.2, 127.5, 125.1, 124.4, 108.3, 61.7, 61.4, 53.5, 14.2, 14.1. HRMS m/z [M+Na]⁺ calcd for C₁₄H₁₆N₂NaO₄S 331.0723, found 331.0732.

1-(Carboxymethyl)-3-(thiophen-2-yl)-1H-pyrazole-5-carboxylic acid (11d). Prepared from 0.01 mol of diester 10d; yield 1.86 g (74%); colorless solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.33 (br.s, 2H), 7.53 (dd, J = 3.6, 1.2 Hz, 1H), 7.51 (dd, J = 5.1, 1.2 Hz, 1H), 7.26 (s, 1H), 7.11 (dd, J = 5.1, 3.6 Hz, 1H), 5.23 (s, 2H). ¹³C NMR (101 MHz, DMSO-d₆) δ 169.7, 161.1, 160.8, 145.4, 135.4, 128.3, 126.1, 125.4, 108.1, 53.6. HRMS m/z [M+Na]⁺ calcd for C₁₀H₈N₂NaO₄S 275.0097, found 275.0108.

Ethyl 3-(tert-butyl)-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-5-carboxylate (10e). The crude substance prepared from 0.02 mol of pyrazole 9e contained only 12% of second regioisomer wasn’t chromatographed prior the hydrolysis step; yield 4.34 g (77%); colorless viscous oil. ¹H NMR (400 MHz, CDCl₃) signals of major regioisomer δ 6.77 (s, 1H), 5.25 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.33 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H).

3-(tert-Butyl)-1-(carboxymethyl)-1H-pyrazole-5-carboxylic acid (11e). The obtained after extraction crude material was recrystallized from MeCN to afford 1.67 g (37% for 2 steps); colorless solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.09 (br.s, 2H), 6.74 (s, 1H), 5.12 (s, 2H), 1.25 (s, 9H). ¹³C NMR (101 MHz, DMSO-d₆) δ 169.9, 161.1, 160.0, 134.0, 107.8, 53.4, 32.1, 30.7. HRMS m/z [M+H]⁺ calcd for C₁₀H₁₅N₂O₄ 227.1026, found 227.1034.
Preparation of anhydrides 12a-e

**General procedure.** To a stirred suspension of diacid 11 (5 mmol) in dry EtOAc (50 mL) was added trifluoroacetic anhydride (10 mmol) and the mixture was stirred at room temperature for 20 h. After evaporation to dryness the residue was triturated with n-hexane (50 mL), filtered and dried in *vacuo* to give pure anhydride 12.

\[
\text{R} - \text{N} = \text{N} - \text{CO}_2H \xrightarrow{\text{(CF}_3\text{CO}_2\text{O, EtOAc, r.t.)}} \text{R} - \text{N} = \text{N} - \text{CO}_2
\]

2-(p-Tolyl)-4H-pyrazolo[5,1-c][1,4]oxazine-4,6(7H)-dione (12a). Prepared from 0.01 mol of diacid 11a; yield 2.37 g (98%); colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.72 (d, \(J = 8.2\) Hz, 2H), 7.42 (s, 1H), 7.29 (d, \(J = 7.9\) Hz, 2H), 5.34 (s, 2H), 2.43 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.8, 154.7, 150.3, 139.4, 129.7, 128.0, 127.2, 125.8, 107.8, 49.2, 21.3.

2-(4-Fluorophenyl)-4H-pyrazolo[5,1-c][1,4]oxazine-4,6(7H)-dione (12b). Prepared from 0.01 mol of diacid 11b; yield 2.39 g (97%); colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.82 (dd, \(J = 8.8, 5.3\) Hz, 2H), 7.41 (s, 1H), 7.17 (t, \(J = 8.7\) Hz, 2H), 5.36 (s, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.4 (d, \(J = 244.5\) Hz), 159.6, 153.7, 150.2, 127.7 (d, \(J = 8.4\) Hz), 127.4, 127.1 (d, \(J = 3.0\) Hz), 116.1 (d, \(J = 21.9\) Hz), 107.7, 49.3.

2-(3,4-Dimethoxyphenyl)-4H-pyrazolo[5,1-c][1,4]oxazine-4,6(7H)-dione (12c). Prepared from 5 mmol of diacid 11c; yield 1.27 g (88%); colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45 (dd, \(J = 3.6, 1.1\) Hz, 1H), 7.39 (dd, \(J = 5.1, 2.0\) Hz, 1H), 6.97 (d, \(J = 8.3\) Hz, 1H), 5.33 (s, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.8, 154.5, 150.3, 150.1, 149.4, 123.6, 118.7, 111.3, 108.7, 107.4, 55.7, 49.2.

2-(Thiophen-2-yl)-4H-pyrazolo[5,1-c][1,4]oxazine-4,6(7H)-dione (12d). Prepared from 5 mmol of diacid 11d; yield 1.15 g (98%); colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45 (dd, \(J = 3.6, 1.1\) Hz, 1H), 7.39 (dd, \(J = 5.1, 1.1\) Hz, 1H), 7.35 (s, 1H), 7.13 (dd, \(J = 5.1, 3.6\) Hz, 1H), 5.34 (s, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.5, 150.0, 149.8, 133.5, 127.9, 127.3, 126.5, 125.7, 107.6, 49.2.
2-(tert-Butyl)-4H-pyrazolo[5,1-c][1,4]oxazine-4,6(7H)-dione (12e). Prepared from 5 mmol of diacid 11e; yield 1.03 g (99%); colorless solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.04 (s, 1H), 5.26 (s, 2H), 1.35 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 165.5, 160.2, 150.5, 126.1, 107.9, 49.1, 32.5, 30.2.

Preparation of compounds 13a-n

General procedure. A mixture of anhydride 12 (0.5 mmol), corresponding imine (0.52 mmol) in dry chlorobenzene (2 mL) was stirred in a screw-cap vial at 130 °C for 16 hours. Upon cooling to room temperature the solvent was removed in vacuo, the residue was dissolved in acetone (10 mL). To the solution were added K$_2$CO$_3$ (1 mmol) and methyl iodide (1 mmol) and the mixture was vigorously stirred at room temperature for 20 hours. The solution was separated from solids, evaporated and the resulting residue was subjected to column chromatography on silica gel.

trans-Methyl 5-ethyl-4-oxo-2,6-di-p-tolyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13a). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 2:1:1); yield 101 mg (50%); colorless amorphous solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.23 (s, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 5.28 (s, 1H), 5.26 (d, J = 1.4 Hz, 1H), 4.22 (dq, J = 14.4, 7.2 Hz, 1H), 3.79 (s, 3H), 2.89 (dq, J = 14.2, 7.1 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.5, 157.1, 153.0, 138.8, 138.2, 135.7, 133.7, 129.9, 129.4, 129.0, 125.6, 104.7, 65.3, 61.7, 53.5, 40.1, 21.3, 21.0, 13.1. HRMS m/z [M+H]$^+$ calcd for C$_{24}$H$_{26}$N$_3$O$_3$ 404.1969, found 404.1986.

trans/cis-Methyl 6-(4-methoxyphenyl)-5-methyl-4-oxo-2-(p-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13b). Eluent for chromatography n-hexane/EtOAc/DCM (from 3:1:1 to 2:1:1); yield 71 mg (35%), dr 20:1; colorless amorphous solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.25 (s, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.23 (d, J = 1.4 Hz, 1H), 5.21 (d, J = 1.4 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.10 (s, 3H), 2.37 (s, 3H). $^{13}$C NMR (101
trans-Methyl 5-methyl-4-oxo-6-phenyl-2-(p-toly)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13c). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 1:1:1): yield 64 mg (34%); colorless amorphous solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.69 (d, \(J = 8.2\) Hz, 2H), 7.38 – 7.31 (m, 3H), 7.26 (s, 1H), 7.21 (d, \(J = 7.9\) Hz, 2H), 7.18 – 7.13 (m, 2H), 5.27 (s, 2H), 3.80 (s, 3H), 3.12 (s, 3H), 2.37 (s, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.5, 157.5, 153.1, 138.8, 135.4, 129.4, 128.9, 127.3, 125.6, 104.9, 64.8, 64.5, 53.7, 33.5, 21.3. HRMS m/z [M+Na\(^+\)] calcd for C\(_{22}\)H\(_{22}\)N\(_3\)NaO\(_3\) 398.1475, found 398.1488.

trans-Methyl 5-butyl-6-(4-nitrophenyl)-4-oxo-2-(p-toly)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13d). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 2:1:1): yield 58 mg (25%); colorless amorphous solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.21 (d, \(J = 8.8\) Hz, 2H), 7.66 (d, \(J = 8.2\) Hz, 2H), 7.39 (d, \(J = 8.7\) Hz, 2H), 7.25 (s, 1H), 7.20 (d, \(J = 7.9\) Hz, 2H), 5.43 (s, 1H), 5.29 (d, \(J = 1.4\) Hz, 1H), 4.26 (dt, \(J = 13.8, 7.9\) Hz, 1H), 3.81 (s, 3H), 2.73 (dt, \(J = 13.6, 6.7\) Hz, 1H), 2.37 (s, 3H), 1.59 – 1.50 (m, 2H), 1.39 – 1.31 (m, 2H), 0.95 (t, \(J = 7.3\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.9, 157.2, 153.5, 148.3, 143.8, 138.6, 135.4, 129.4, 128.9, 127.3, 125.6, 124.6, 105.3, 64.7, 61.6, 53.8, 45.0, 30.0, 21.3, 19.8, 13.7. HRMS m/z [M+Na\(^+\)] calcd for C\(_{24}\)H\(_{26}\)N\(_4\)NaO\(_5\) 485.1795, found 485.1815.

trans-Methyl 2-(4-fluorophenyl)-6-(4-methoxyphenyl)-4-oxo-5-propyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13e). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 2:1:1): yield 136 mg (62%); colorless viscous oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.77 (dd, \(J = 8.9, 5.4\) Hz, 2H), 7.21 (s, 1H), 7.14 – 7.01 (m, 4H), 6.85 (d, \(J = 8.8\) Hz, 2H), 5.26 (d, \(J = 1.4\) Hz, 1H), 5.23 (d, \(J = 1.4\) Hz, 1H), 4.16 (dt, \(J = 11.5, 7.9\) Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.73 (ddd, \(J = 13.6, 8.2, 5.3\) Hz, 1H), 1.66 – 1.49 (m, 2H), 0.92 (t, \(J = 7.4\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.4, 162.9 (d, \(J = 247.5\) Hz), 160.0, 157.3, 152.0, 135.9, 128.4 (d, \(J = 3.2\) Hz), 128.4, 127.5 (d, \(J = 8.2\) Hz), 127.3, 115.6 (d, \(J = 21.7\) Hz), 114.7, 104.7, 65.3, 61.7, 55.3, 53.5, 46.6, 21.2, 11.0. HRMS m/z [M+Na\(^+\)] calcd for C\(_{24}\)H\(_{26}\)FN\(_3\)NaO\(_4\) 460.1643, found 460.1640.
trans-Methyl 5-allyl-2-(4-fluorophenyl)-6-(3-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13f). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 2:1:1); yield 54 mg (24%); colorless viscous oil. \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) δ 7.77 (dd, \( J = 8.9, 5.3 \) Hz, 2H), 7.28 – 7.24 (m, 1H), 7.24 (s, 1H), 7.09 (t, \( J = 8.7 \) Hz, 2H), 6.85 (ddd, \( J = 8.3, 2.5, 0.8 \) Hz, 1H), 6.76 – 6.71 (m, 1H), 6.67 (t, \( J = 2.1 \) Hz, 1H), 5.75 (dddd, \( J = 17.1, 10.1, 8.0, 4.4 \) Hz, 1H), 5.29 (ddd, \( J = 10.3, 2.3, 1.5 \) Hz, 1H), 5.29 (d, \( J = 1.4 \) Hz, 1H), 5.25 (d, \( J = 1.3 \) Hz, 1H), 5.25 – 5.19 (m, 1H), 5.01 (ddt, \( J = 15.3, 4.3, 1.7 \) Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.25 (ddt, \( J = 15.4, 8.0, 0.9 \) Hz, 1H). \( ^{13} \)C NMR (101 MHz, CDCl\(_3\)) δ 168.1, 162.9 (d, \( J = 24.7 \) Hz), 160.3, 156.9, 152.2, 138.0, 135.7, 132.1, 130.5, 128.4 (d, \( J = 3.2 \) Hz), 127.5 (d, \( J = 8.2 \) Hz), 119.2, 118.2, 115.6 (d, \( J = 21.7 \) Hz), 114.0, 112.2, 105.0, 64.9, 60.8, 55.3, 53.5, 46.7. HRMS m/z [M+H]\(^+\) calcd for C\(_{24}\)H\(_{23}\)FN\(_3\)O\(_4\) 436.1667, found 436.1677.

\[
\begin{align*}
&\text{MeO} \quad \text{Et} \\
&\text{O} \\
&\text{Me}_2\text{C} \quad \text{Me}
\end{align*}
\]

trans-Methyl 2-(3,4-dimethoxyphenyl)-5-ethyl-4-oxo-6-(p-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13g). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 2:1:1); yield 97 mg (43%); colorless viscous oil. \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) δ 7.34 (d, \( J = 2.0 \) Hz, 1H), 7.31 (dd, \( J = 8.3, 2.0 \) Hz, 1H), 7.19 (s, 1H), 7.12 (d, \( J = 8.1 \) Hz, 2H), 7.05 (d, \( J = 8.2 \) Hz, 2H), 6.88 (d, \( J = 8.3 \) Hz, 1H), 5.26 (s, 1H), 5.25 (d, \( J = 1.3 \) Hz, 1H), 4.21 (dq, \( J = 14.4, 7.2 \) Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.78 (s, 3H), 2.87 (dq, \( J = 14.2, 7.1 \) Hz, 1H), 2.29 (s, 3H), 1.15 (t, \( J = 7.2 \) Hz, 3H). \( ^{13} \)C NMR (101 MHz, CDCl\(_3\)) δ 168.5, 157.1, 152.8, 149.3, 149.1, 138.8, 135.8, 133.7, 129.9, 126.0, 125.7, 118.5, 111.2, 108.8, 104.5, 65.2, 61.7, 55.93, 55.89, 53.5, 40.1, 21.0, 13.1. HRMS m/z [M+H]\(^+\) calcd for C\(_{25}\)H\(_{28}\)N\(_3\)O\(_5\) 450.2023, found 450.2032.

\[
\begin{align*}
&\text{MeO} \quad \text{Me} \\
&\text{O} \\
&\text{Me}_2\text{C} \quad \text{Me}
\end{align*}
\]

trans-Methyl 5-cyclopropyl-2-(3,4-dimethoxyphenyl)-4-oxo-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13h). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 2:1:1); yield 68 mg (30%); colorless viscous oil. \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) δ 7.39 – 7.30 (m, 5H), 7.24 – 7.21 (m, 3H), 7.21 (s, 1H), 6.90 (d, \( J = 8.3 \) Hz, 2H), 5.36 (s, 1H), 5.30 (d, \( J = 1.4 \) Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H), 2.79 – 2.72 (m, 1H), 1.17 – 1.09 (m, 1H), 0.91 – 0.83 (m, 1H), 0.82 – 0.74 (m, 1H), 0.60 – 0.53 (m, 1H). \( ^{13} \)C NMR (101 MHz, CDCl\(_3\)) δ 168.4, 159.0, 152.8, 149.4, 149.2, 136.9, 135.9, 129.3, 128.8, 126.0, 125.0, 118.6, 111.2, 108.8, 104.8, 65.1, 64.0, 55.96, 55.94, 53.5, 29.0, 9.3, 6.2. HRMS m/z [M+H]\(^+\) calcd for C\(_{25}\)H\(_{26}\)N\(_3\)O\(_5\) 448.1867, found 448.1881.
**trans-Methyl 5-ethyl-4-oxo-2-(thiophen-2-yl)-6-(p-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13i).** Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 3:1:1); yield 111 mg (56%); colorless viscous oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (dd, $J = 3.6, 1.1$ Hz, 1H), 7.25 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.15 (s, 1H), 7.12 (d, $J = 8.1$ Hz, 2H), 7.08 – 7.01 (m, 3H), 5.27 (s, 1H), 5.25 (d, $J = 1.4$ Hz, 1H), 4.21 (dq, $J = 14.4, 7.2$ Hz, 1H), 3.78 (s, 3H), 2.87 (dq, $J = 14.2, 7.1$ Hz, 1H), 2.29 (s, 3H), 1.15 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.3, 156.8, 148.2, 138.8, 135.9, 135.2, 133.5, 129.9, 127.5, 125.9, 125.2, 124.7, 104.7, 65.2, 61.7, 53.5, 40.1, 21.0, 13.1. HRMS m/z [M+H]$^+$ calcd for C$_{21}$H$_{22}$N$_3$O$_5$S 396.1376, found 396.1379.

**trans-Methyl 6-(4-chlorophenyl)-4-oxo-5-propyl-2-(thiophen-2-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13j).** Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 3:1:1); yield 47 mg (22%); colorless viscous oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38 (dd, $J = 3.6, 1.1$ Hz, 1H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.28 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.16 (s, 1H), 7.12 (d, $J = 8.5$ Hz, 2H), 7.07 (dd, $J = 5.1, 3.6$ Hz, 1H), 5.28 (s, 1H), 5.23 (d, $J = 1.3$ Hz, 1H), 4.16 (dt, $J = 13.8, 7.9$ Hz, 1H), 3.80 (s, 3H), 2.71 (ddd, $J = 13.6, 8.3, 5.2$ Hz, 1H), 1.65 – 1.50 (m, 2H), 0.92 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.1, 157.1, 148.5, 135.7, 135.0, 135.02, 135.02, 129.6, 127.6, 127.5, 125.4, 124.8, 105.0, 64.9, 61.6, 53.7, 46.7, 21.2, 11.0. HRMS m/z [M+H]$^+$ calcd for C$_{21}$H$_{22}$ClN$_3$O$_5$S 430.0987, found 430.0999.

**trans-Methyl 5-allyl-6-(3-methoxyphenyl)-4-oxo-2-(thiophen-2-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13k).** Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1:1 to 3:1:1); yield 116 mg (55%); colorless viscous oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (dd, $J = 3.6, 1.2$ Hz, 1H), 7.27 – 7.22 (m, 1H), 7.18 (s, 1H), 7.06 (dd, $J = 5.1, 3.6$ Hz, 1H), 6.84 (ddd, $J = 8.3, 2.5, 0.8$ Hz, 1H), 6.73 (ddt, $J = 7.7, 1.5, 0.7$ Hz, 1H), 6.66 (t, $J = 2.2$ Hz, 1H), 5.74 (ddddd, $J = 17.1, 10.2, 8.0, 4.4$ Hz, 1H), 5.28 (d, $J = 1.4$ Hz, 1H), 5.30 – 5.25 (m, 1H), 5.23 (s, 1H), 5.24 – 5.18 (m, 1H), 4.99 (ddt, $J = 15.3, 4.4, 1.7$ Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.24 (ddt, $J = 15.3, 8.0, 0.9$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.0, 160.3, 156.8, 148.4, 137.8, 135.7, 135.1, 132.1, 130.5, 127.6, 125.3, 124.8, 119.2, 118.2, 114.0, 112.1, 105.0, 64.8, 60.8, 55.3, 53.5, 46.7. HRMS m/z [M+H]$^+$ calcd for C$_{22}$H$_{22}$N$_3$O$_5$S 424.1326, found 424.140.
trans-Methyl 2-(tert-butyl)-4-oxo-5-propyl-6-(p-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13l). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1 to 3:1:1); yield 134 mg (70%); colorless viscous oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.13 (d, $J$ = 7.9 Hz, 2H), 7.02 (d, $J$ = 8.0 Hz, 2H), 6.82 (s, 1H), 5.20 (s, 1H), 5.18 (s, 1H), 4.13 (dt, $J$ = 13.8, 7.9 Hz, 1H), 3.77 (s, 3H), 2.67 (ddd, $J$ = 13.5, 8.2, 5.3 Hz, 1H), 2.32 (s, 3H), 1.65 – 1.46 (m, 2H), 1.29 (s, 9H), 0.89 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.8, 163.8, 157.7, 138.6, 134.9, 129.8, 126.1, 104.7, 64.8, 61.9, 53.3, 46.5, 32.2, 30.4, 21.2, 21.0, 11.0. HRMS m/z [M+H]$^+$ calcd for C$_{22}$H$_{30}$N$_3$O$_3$ 384.2282, found 384.2293.

trans/cis-Methyl 2-(tert-butyl)-5-butyl-6-(3,4-dimethoxyphenyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13m). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1 to 2:1:1); yield 118 mg (53%), dr 20:1; colorless amorphous solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.82 (s, 1H), 6.78 (d, $J$ = 8.3 Hz, 1H), 6.69 (dd, $J$ = 8.3, 2.2 Hz, 1H), 6.48 (d, $J$ = 2.2 Hz, 1H), 5.16 (d, $J$ = 1.5 Hz, 1H), 5.15 (d, $J$ = 1.5 Hz, 1H), 4.16 (dt, $J$ = 13.7, 7.8 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 2.71 (dt, $J$ = 13.6, 6.6 Hz, 1H), 1.55 – 1.47 (m, 2H), 1.37 – 1.23 (m, 2H), 1.29 (s, 9H), 0.92 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.8, 163.8, 157.5, 149.5, 149.4, 134.8, 129.3, 118.9, 111.2, 108.8, 104.4, 64.8, 61.9, 55.9, 55.8, 53.3, 44.4, 32.3, 30.4, 30.0, 19.8, 13.8. HRMS m/z [M+H]$^+$ calcd for C$_{24}$H$_{34}$N$_3$O$_5$ 444.2493, found 444.2490.

trans-Methyl 2-(tert-butyl)-5-isopropyl-6-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-7-carboxylate (13n). Eluent for chromatography n-hexane/EtOAc/DCM (from 5:1 to 3:1:1); yield 128 mg (64%); colorless viscous oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.06 (d, $J$ = 8.7 Hz, 2H), 6.82 (s, 1H), 6.80 (d, $J$ = 8.8 Hz, 2H), 5.24 (d, $J$ = 1.1 Hz, 1H), 5.07 (d, $J$ = 1.5 Hz, 1H), 4.96 (hept, $J$ = 6.8 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 1.28 (s, 9H), 1.16 (d, $J$ = 6.7 Hz, 3H), 0.91 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.6, 163.7, 159.5, 157.3, 135.3, 130.9, 127.2, 114.3, 104.5, 65.7, 57.3, 55.2, 53.2, 44.9, 32.2, 30.4, 20.6, 20.0. HRMS m/z [M+H]$^+$ calcd for C$_{22}$H$_{30}$N$_3$O$_4$ 400.2231, found 400.2235.
**Crystallographic data for compounds 13a and 13m**

Suitable crystals of 13a and 13m were studied using Xcalibur, Eos diffractometer (monochromated MoKα radiation, λ = 0.71073 Å). In all cases the temperature was kept at 100(2) K. In each case the structure has been solved with the ShelXT [5] structure solution program using Intrinsic Phasing and refined with the ShelXL [6] refinement package incorporated in the OLEX2 program package [6] using Least Squares minimization. Empirical absorption correction was applied in CrysAlisPro [7] program complex using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

**Table S1. Crystal data and structure refinement for 13a and 13m**

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References


$^1$H and $^{13}$C NMR of compound 10a
$^1$H and $^{13}$C NMR of compound 11a
$^1\text{H}$ and $^{13}\text{C}$ NMR of compound 10b

![NMR spectra](image)

S16
$^1$H and $^{13}$C NMR of compound 11b
$^1$H and $^{13}$C NMR of compound 10c
$^1$H and $^{13}$C NMR of compound 11c
$^1$H and $^{13}$C NMR of compound 10d
$^1$H and $^{13}$C NMR of compound 11d
$^{1}H$ and $^{13}C$ NMR of compound 11e
$^1$H and $^{13}$C NMR of compound 12a

![NMR Spectra](image-url)
$^1$H and $^{13}$C NMR of compound 12b
$^1$H and $^{13}$C NMR of compound 12c
$^1\text{H}$ and $^{13}\text{C}$ NMR of compound 12d
$^1$H and $^{13}$C NMR of compound 12e
$^1$H and $^{13}$C NMR of compound 13a
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$^1$H and $^{13}$C NMR of compound 13c
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$^1$H and $^{13}$C NMR of compound 13j
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$^1$H and $^{13}$C NMR of compound 13l
$^{1}$H and $^{13}$C NMR of compound 13m
$^{1}\text{H}$ and $^{13}\text{C}$ NMR of compound 13n

[Chemical structure image]